RB and Prognosis in Resected Lung Adenocarcinoma
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The treatment of resected lung adenocarcinoma has ample room for improvement. Can genomic characterization aid in deciding how and when to apply adjuvant therapy in the smallest resected tumors? Clin Cancer Res; 21(11); 2418–20. ©2015 AACR.
See related article by Choi et al., p. 2613

In this issue of Clinical Cancer Research, Choi and colleagues (1) examine the impact that histology and coding mutations have on the long-term outcome of 247 lung adenocarcinoma cases that were resected in Korea. Non–small cell lung cancer (NSCLC) is the most important cause of cancer mortality worldwide, and lung adenocarcinoma is the most common histologic variant of the disease. This study represents the first drops of what will surely be an ensuing downpour of genomic data derived from “real-life” clinical cohorts, and in this respect picks up where large-scale, disease-focused genomic projects initiated by The Cancer Genome Atlas (TCGA), the International Cancer Genome Consortium (ICGC), and several larger private collections of retrospectively collected tumors have left off.

The advent of next-generation sequencing technology has allowed us to sequence tumor and normal DNA quickly, accurately, and inexpensively. Improvements in nucleic acid isolation and library generation chemistry have allowed us to do so from clinical samples, capturing and resequencing all the coding exons in the human genome reproducibly in many centers across the world. Finally, algorithmic advances in automated mutation calling have made the data analysis practicable in many international centers of excellence. In other words, unbiased, large-scale tumor/normal resequencing can now be done in many places in the world. The question now is “When should it be done?”, both to address pressing clinical questions and to affect the management of individual patients. Discovery of new and important mutations can and does still happen, but in heavily resequenced tumor types, such as melanoma, NSCLC, and leukemias, we know most major drivers at the genome level in these diseases and new discoveries based on sequencing alone will require thousands, not hundreds, of additional tumors (2).

Our focus is shifting then to applying next-generation sequencing technologies to clinically relevant datasets, from which we might gain important insights into how to treat patients differently. Whereas the management of metastatic NSCLC has been revolutionized by the recognition of recurrent driver oncogenes, coupled with our increasing ability to target these gain of function molecules with drugs, resected lung adenocarcinoma has not yet benefited from this revolution in personalized medicine. The need is great in this subset of patients, because anywhere from 50% to 70% of patients will recur and die of their disease, despite a technically successful resection of their primary tumor. As such, adjuvant therapy holds great promise, but has been unevenly applied in the community. Currently, adjuvant cytotoxic chemotherapy is recommended for patients with stage II and IIIA resected lung adenocarcinoma, and some stage IA patients, but its use is tempered in a medically frail patient population due to a perceived lack of benefit in the community, despite good evidence to the contrary. Unlike the scenario in resected breast (3) and colorectal cancers (4), multigene mRNA signatures (5–7) have not yet taken root as valuable decision-making aids in resected lung adenocarcinoma.

Through an unbiased examination of the coding sequences and copy-number profiles of 247 patients with lung adenocarcinoma, Choi and colleagues (1) bring DNA sequence and copy number into play as a potential decision-making aids in early, resected lung adenocarcinoma. They begin with a discovery cohort of 170 patients with resected lung adenocarcinoma, of whom 65% had stage IA disease. This sample set is especially valuable because the stage IA population is an especially heterogeneous one for whom adjuvant therapy is not routinely recommended (8). The authors detected 22 significantly mutated genes, some overlapping with those reported in other studies (9–11) with some expected and unexpected exceptions. First, because neither whole-genome sequencing nor RNAseq was performed, the investigators did not identify any fusion genes in ALK, RET, ROS1, or NTRK1. In addition, the incidence of some known drivers, such as those in KRAS, was surprisingly low (6%), possibly due to sample purity, insufficient depth of sequencing, or both. Despite maneuvers to increase sensitivity of mutation detection through fine-tuning mutation calling algorithms (12), many of these probably artifically low rates of mutation remained, despite the background (passenger)
mutation rate increasing. This experience reinforces the powerful effects that the high background mutation rate in lung adenocarcinoma has on mutational significance, a problem exacerbated by sequencing with lower-than-needed depth of coverage, especially across key genes such as KRAS.

After evaluating and addressing, to as large an extent as possible, these technical issues, the authors then tackled the clinical questions relevant to the patients whose tumors comprised their dataset. They focused on the stage IA patient population introduced above, correctly recognizing that the management of this heterogeneous group is especially challenging due to the high recurrence rate, coupled with a lack of established adjuvant therapy benefit in this population (8), leading to a decision-making paralysis in the treating physician. Their training set suggested that stage IA patients with defects in the RB pathway had a worse prognosis after resection than did those patients with the RB pathway intact (Fig. 1). The validation set of tumors confirmed both the directionality of the finding in resected lung adenocarcinoma and the stage IA specificity of it.

The RB1 gene product is a major convergence point for many G1–S cell-cycle decisions. Because the topology of the pathway is largely known, the authors evaluated the phosphoprotein (inactive) levels of RB1, and the protein levels of E2F1, cyclins D1 and E1, in an effort to construct an immunohistochemistry-based assay using this pathway. Those efforts confirmed that the major members of this pathway behave as expected at the protein level, if the mutation and copy-number status of RB1 itself is known, setting the stage for a focused interrogation using a few antibodies and a targeted sequencing panel in stage IA resected lung adenocarcinoma.

This work greatly advances our understanding of the mutational landscape of lung adenocarcinoma, especially in Asian patients, but more work remains. With respect to characterization, deeper sequencing might show us that Asian and North American patients with lung adenocarcinoma are more alike than different. Capturing the fusion status of this or similar cohorts might educate us as to whether just as we expect more EGFR mutations in Asian patients, should we likewise expect more fusion kinases as well. Finally, RNA analysis would tell us how overlapping or
independent the effects of RB loss are on the transcriptional prognostic profiles of lung adenocarcinoma. That said, this dataset is an important foundation upon which we all can build to focus therapy where it is most needed in patients with resected lung adenocarcinoma.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References
